PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
100994-1 WO		

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/000695	23.02.2004	25.02.2003

International Patent Classification (IPC) or national classification and IPC
C07D281/10, C07D337/08, A61K31/38, A61K31/554, A61P3/06

Applicant
ASTRAZENECA AB

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 12 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 14 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24.08.2004	20.12.2004

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Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-56 as originally filed

   Claims, Numbers

   1-25 filed with telefax on 06.10.2004

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

10/546695 International application No. PCT/GB2004/000695

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 17 with regard to industrial applicability

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 17 with regard industrial applicability

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-25
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-25
Industrial applicability (IA)	Yes:	Claims	1-16,18-25
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III.

Claim 17 is directed to methods for treatment of the human or animal body by surgery or therapy. It relates to subject-matter considered by the ISA to be covered by the provisions of Rule 67.1(iv) PCT.

For the assessment of the present claim 17 on the question whether its subject-matter is industrially applicable, no unified criteria exist in the PCT Contracting States. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34 (4) (a)(i) PCT). The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treament and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Under the terms of Rule 39.1(iv) PCT, the ISA was not required to carry out a search of such claims, but as indicated in the ISR, the search was carried out and based on the alleged effects of the compounds. Similarly, the IPEA (which is the ISA) is not required to carry out an International preliminary examination of such claims, but as for the ISR, the IPER will be based on the alleged effects of the compounds (Rule 67.1 (iv) PCT).

Re Item V.

1. Limitations

The scope of the current application is not appropriately defined on account of the use of non-specific terms like prodrugs and of unlimited definitions like aryl, heteroaryl, heterocyclyl, carbocyclyl, alkylene, alkenylene, alkyl, acyl, etc, and derivatives thereof. Indeed, the claims encompass a very large number of possible embodiments while the description discloses, and provides support for, only a relatively small proportion of those embodiments (articles 5 and 6 PCT).

Consequently the non-compliance with the substantive provisions is to such an extent, that a meaningfull search of the whole claimed subject-matter of claim 1 could not be carried out (PCT Guidelines, 9.19 and 9.23). The search was therefore limited to a reasonable generalisation of the examples (see also point 4.4).

The Applicant is aware that no examination can be performed on a subject-matter that has not been searched. As to the term prodrugs, the search includes this term as far as it is covered by formula (I).

2. Cited documents

D1: WO 03/022825
D2: DATABASE CAPLUS; NAGASE, TOSHIO ET AL retrieved from STN Database accession no. 2002:521715 (WO 02/053548)
D3: WO 02/08211
D4: WO 00/47568
D5: WO 00/01687
D6: WO 97/33882
D7: WO 96/05188
D8: WO 96/08484
D9: LEWIS M C ET AL: JOURNAL OF LIPID RESEARCH, vol. 36, no. 5, May 1995, pages 1098-1105
D10: EP 0 864 582

3. Novelty

3.1 The intermediate document D1 is relevant for the purposes of Rules 33.1 c, 64.3 and 70.10 PCT. The priority document has been checked. The present application appears fully entitled to the claimed priority date. Note that D1 discloses a synthetic compound which falls in the presently claimed scope and, in an eventually further European/national phase, it would have to be disclaimed.

3.2 In his reply dated 06.10.04 to the written opinion of the ISA, the Applicant has filed an amendment in order to disclaim the two compounds of D2 mentioned in the search report. These compounds are also pharmacologically active in lowering blood glucose level and therefore useful as diabetes remedies or antiobesity agents. In spite of the closeness with the pending application, no common disease is explicitely indicated and therefore D2 does not seem to be relevant for the inventive step question (point 4).

3.3 D3 to D8 overlap in various ways the presently claimed scope although not disclosing specific compounds. There is an overlap:

- with D3 wherein j = 2; R^{1A}, R^{1B} = H; R^{2A}, R^{2B} = H, alkyl, alkenyl; Z = CHR^4 (R^4 is optionally substituted phenyl - substituents covered by the R^3 definitions of the present application); Y = NR^3; m = 1 to 4; R^6 can represent a chain like (IA), (IA)+(IB) or (IA)+(IB)+(IC) of the application, including peptidic groups (see, e.g., R^6 = ...OR^{13}; $NR^{13}R^{14}$; $NR^{14}COR^{13}$; $CONR^{13}R^{14}$... amino acid residue; peptide residue, etc).

- with D4 wherein R^N = H, alkyl; R^1, R^2 = H, akyl, alkenyl; R^3, R^4 when they overlap R^{22}, R^{23} of the present application; R^5 = H, R^6 = optionally substituted phenyl (substituents covering the R^3 definitions of the present application); q = 1 to 4; R^x can represent a chain like (IA), (IA)+(IB) or (IA)+(IB)+(IC) of the application, including peptidic groups (see, e.g., R^x = ...OR^{13}; SR^{13}; $NR^{13}R^{14}$; $NR^{14}COR^{13}$; $CONR^{13}R^{14}$... amino acid residue; peptide residue, etc).

- with D5 wherein n = 2; R^7, R^8 = H; R^1, R^2 = H, alkyl, alkenyl; R^3, R^4 when they overlap R^{22}, R^{23} of the present application; R^5 = H, R^6 = optionally substituted phenyl (substituents covering the R^3 definitions of the present application); q = 1 to 4; R^x can represent a chain like (IA), (IA)+(IB) or (IA)+(IB)+(IC) of the application, including peptidic groups (see, e.g., R^x = ...OR^{13}; SR^{13}; $NR^{13}R^{14}$; $NR^{14}COR^{13}$; $CONR^{13}R^{14}$... amino acid residue; peptide residue, etc).

- with D6 wherein n = 2; R^7, R^8 = H; R^1, R^2 = H, alkyl, alkenyl; R^3, R^4 when they overlap R^{22}, R^{23} of the present application; q = 1 to 4; R^x can represent a chain like (IA), (IA)+(IB) or (IA)+(IB)+(IC) of the application, including peptidic groups (see, e.g., R^x = ...OR^{13}; SR^{13}; $NR^{13}R^{14}$; $NR^{14}COR^{13}$; $CONR^{13}R^{14}$... amino acid residue; peptide residue, etc).

- with D7 wherein R^9, R^{10} = H; R^1, R^2 = alkyl; R^3 = H, OH, alkyl, alkoxy; R^4 = optionally substituted phenyl; R^6, R^7 = optionally substituted alkyl, optionally substituted alkoxy; R^5, R^8 = when they overlap R^4, R^7 of the present application.

- with D8 wherein n = 2; R_1, R_2 = H, alkyl; R^3, R^4 when they overlap R^{22}, R^{23} of the present application; R^5 = optionally substituted phenyl (substituents covering the R^3 definitions of the present application), R^6 = H; q = 1 to 4; X = alkyl, OR, SR.

D9 and D10 are background art documents.

3.4 Thanks to the specific disclaimers, the novelty has been formally restored but this is unsufficient to stress unambiguously the feature(s) which is(are) responsable for the novelty of the whole claimed domain especially because of the overlaps with prior art documents. Such characteristic feature(s) must be common to all the compounds claimed in order to satisfy the requirement of unity.

4. Inventive step

4.1 According to the description, the problem underlying the present invention is to provide benzothiazepine and benzothiepine derivatives useful for the treatment of diseases associated with hyperlipidaemic conditions. The compounds disclosed in the cited relevant documents D3 to D8 have the same applications.

4.2 Due to the overlaps of the presently claimed scope with the prior art documents, a skilled person can without particular inventive effort combine the various and large teachings of this prior art, select combinations and come straightforwardly to the present invention.

4.3 Several remarks should be made in relation with the Applicant's reply of 06.10.04.

(1) In order to demonstrate the presence of an unexpected effect, the Applicant has brought IBAT(human) IC_{50} µM results and chose as comparative references compounds of WO 03/020710 (now designated as D11). Normally D11 is not relevant for the purpose of

inventive step because it was published too late. This choice could be admissible if these compounds were actually the structurally closest prior art compounds. This is not the case. If the Applicant were willing to take most appropriate comparison references out of his own applications (even published too late), he should have been logically expected to take D1 cited aboved, and especially the compounds mentioned in the ISR. Nevertheless, simply considering the citations of applications published in time, any document which overlaps with the present application represents a prior art closer than D11;

(2) The teaching of the overlapping prior art confirms the general knowledge of the skilled person that the ring members -N- and -CH- are bio-isosterically exchangeable and that, consequently, the desired property is expected to be maintained. It is noted incidentally that the data provided within the Applicant's reply of 06.10.04 do not show any significant difference between the two groups of compounds (appendix I vs. appendix II) which give results in the same range of magnitude. It is noted that the examples 1 to 4 of the appendix II are not identified. Their numbering has been supposed to correspond to the one of the application: a consequence is that the tested illustration is very specific and limited to compounds carrying on the 7- or 8-positions a chain containing two peptidic bonds [corresponding to figure (IB), *i.e.* (IA)+(IB)] and wherein m and q = 0, p = 2, r = 3; R^4, R^7, R^8, R^9, R^{21}, R^{23}, R^{24} = H and Z = O or S.

(3) the Applicant has not provided informations or amendments which would allow to distinguish clearly the presently claimed domain, *i.e.* which would help to identify the essential characteristic of the present invention; the presence of an inventive step should have been shown by an unexpected effect which is clearly linked to the common structural feature on the basis of which the novelty has been recognized. Presently it does not appear to be surprising that the presently claimed compounds are active since they can be considered as selected from the state of the art;

(4) the appreciation of how narrowly or broadly defined may be a claimed scope is very dependent on the closeness of the state of the art. It is obvious that, if the state of the art is so close that compound disclaimers are mandatory and that large overlaps are encountered, the extent of the generalization is relatively limited.

4.4 The Applicant's attention is drawn to the fact that the claims as presently drafted do

not fully satisfy PCT requirements. Particularly, the protection which is sought should comply with a reasonable breadth of a scope covering only variants which solve the problem underlying the invention.

It is realized that the Applicant is entitled to claim all obvious modifications of what was concretely described, *i.e.* a certain number of examples, and that alternative variations have to be supported by the description.

Open expressions or terms, particularly *carbocyclyl, heterocyclyl, etc*, derivatives thereof used throughout the claims without further definitive qualifications and undefined terms like *prodrugs* and/or the irrealistic amount of claimed substituents for all variants extend the scope of the claims beyond what has actually been investigated by the inventor(s). They render the claims **obscure in scope** and do not allow to correctly define a scope for which protection can actually be granted.

Concerning the term "prodrugs", it is noted that such a term does not provide any technical indication with regard to the structure of the corresponding compounds and encompasses any inactive functional derivatives able, or at least likely to be able, to convert into a final drug, therefore requiring undue *in vivo* experimentation in order to determine which compounds are inactive prodrugs. The term "prodrug" is thus an attempt to define claimed compounds by reference to a desirable characteristic or property (a result to be achieved). In other words, as actually the Applicant recognizes it, it is a functional definition instead of a structural specification and functional definitions can only exceptionally be accepted if there is no other way to better define the term, like structural definitions usually do. The application provides support within the meaning of article 6 PCT and disclosure within the meaning of article 5 PCT for only a very limited number of compounds. Since the disputed term may encompass forms which are not solution of the problem, suitable definitions as given in the description should have been incorporated in the claims where relevant (It is recalled to the preliminary remark about the limitation made at the level of the search which also applies to the substantive examination).

In view of the given illustrations of the examples, (quasi-)unlimited definitions appear ***speculative***. Presently all prepared and tested compounds correspond to a definite structure (see point 4.3 (2) above). This basic common structure being also known in the

prior art (cf. overlaps), it can be questioned whether such a common core is also a necessary characteristic of the invention which should not be allowed to vary out of a ***reasonable*** extent of the usual equivalents and (bio)isosters of these variants.

The extent of a "reasonable generalisation" also depends on the extent of the illustration and also upon the relative distance to the prior art compounds which presently is very close because of the overlaps.

There is indeed a great variety of structural possibilities which are claimed and not yet explored by the Applicant; the *effect of which cannot be foreseen* having regard to the problem underlying the present application. The meanings of the substituents are also to be considered in view of the reproducibility and the feasablity of the invention in all its claimed aspects. Thus it cannot be ascertained that all the encompassed compounds fall within the scope of the claims of the present application and/or constitute actual solutions to the problem.

Chemical species could have been precisely defined for the disputed expressions or terms by means of the definitions given in the specification.

In conclusion, the inventive step required by Article 33 (3) PCT can be acknowledged only for a well-defined scope embracing a reasonable generalisation of the very invention as illustrated. It should be credible that the unexpected effect on which the acknowledgment of an inventive step is based concerns also all the claimed compounds.

5. Miscellaneous

5.1 The process claim 13 is directed to a plurality of processes. It has not been redrafted in order for each process to be the subject-matter of a different claim.

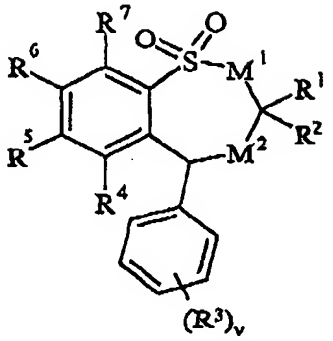
5.2 It is noted that the description may be misleading as it says that many of the intermediates described are provided as a further feature of the invention: (1) these compounds are not claimed as such; (2) if the invention is to be understood as based on the compounds of formula (I), the description contains contradictory statements which

should have been avoided since compounds are said to be active and belong eventually to another invention.

5.3 An inconsistency is noted by defining v. If v = 0, R^3 does not exist, and no substituent is on the phenyl group, unless a radical or a charge is meant and, in such a case, the counterion should be given. The inconsistency lies in the fact that, where hydrogen is a possible substituent in other group definitions, it is expressly mentioned.

Claims

1. A compound of formula (I):



(I)

wherein

M^1 is $-CH_2-$ or $-NR^{21}-$;

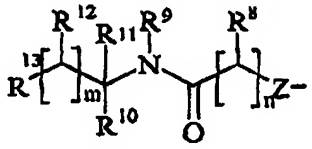
M^2 is $-CR^{22}R^{23}-$ or $-NR^{24}-$; provided that if M^1 is $-NR^{21}-$, M^2 is $-CR^{22}R^{23}-$;

One of R^1 and R^2 are selected from hydrogen, C_{1-6}alkyl or C_{2-6}alkenyl and the other is selected from C_{1-6}alkyl or C_{2-6}alkenyl;

R^3 is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl and *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl;

v is 0-5;

one of R^5 and R^6 is a group of formula (IA):



(IA)

R^4 and R^7 and the other of R^5 and R^6 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl,

100994 PCT Amended Claims

N-(C_{1-4}alkyl)sulphamoyl and *N*,*N*-(C_{1-4}alkyl)$_2$sulphamoyl; wherein R^4 and R^7 and the other of R^5 and R^6 may be optionally substituted on carbon by one or more R^{25};

Z is -O-, -N(R^a)-, -S(O)$_b$- or -CH(R^n)-; wherein R^a is hydrogen or C_{1-6}alkyl and b is 0-2;

R^8 is hydrogen, C_{1-4}alkyl, carbocyclyl or heterocyclyl; wherein R^8 may be optionally substituted on carbon by one or more substituents selected from R^{26}; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{27};

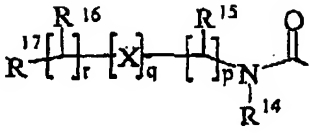
R^9 is hydrogen or C_{1-4}alkyl;

R^{10} and R^{11} are independently selected from hydrogen, C_{1-4}alkyl, carbocyclyl or heterocyclyl; or R^{10} and R^{11} together form C_{2-6}alkylene; wherein R^{10} and R^{11} or R^{10} and R^{11} together may be independently optionally substituted on carbon by one or more substituents selected from R^{28}; and wherein if said heterocyclyl contains an -NH- moiety, that nitrogen may be optionally substituted by one or more R^{29};

R^{12} is hydrogen, C_{1-4}alkyl, carbocyclyl or heterocyclyl; wherein R^{12} may be optionally substituted on carbon by one or more substituents selected from R^{30}; and wherein if said heterocyclyl contains an -NH- moiety, that nitrogen may be optionally substituted by one or more R^{31};

R^{13} is hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxy, C_{1-10}alkoxycarbonyl, C_{1-10}alkanoyl, C_{1-10}alkanoyloxy, *N*-(C_{1-10}alkyl)amino, *N*,*N*-(C_{1-10}alkyl)$_2$amino, *N*,*N*,*N*-(C_{1-10}alkyl)$_3$ammonio, C_{1-10}alkanoylamino, *N*-(C_{1-10}alkyl)carbamoyl, *N*,*N*-(C_{1-10}alkyl)$_2$carbamoyl, C_{1-10}alkylS(O)$_a$ wherein a is 0 to 2, *N*-(C_{1-10}alkyl)sulphamoyl, *N*,*N*-(C_{1-10}alkyl)$_3$sulphamoyl, *N*-(C_{1-10}alkyl)sulphamoylamino, *N*,*N*-(C_{1-10}alkyl)$_2$sulphamoylamino, C_{1-10}alkoxycarbonylamino, carbocyclyl, carbocyclylC_{1-10}alkyl, heterocyclic group, heterocyclylC_{1-10}alkyl, carbocyclyl-(C_{1-10}alkylene)$_e$-R^{32}-(C_{1-10}alkylene)$_f$- or heterocyclyl-(C_{1-10}alkylene)$_g$-R^{33}-(C_{1-10}alkylene)$_h$-; wherein R^{13} may be optionally substituted on carbon by one or more substituents selected from R^{36}; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{37}; or R^{13} is a group of formula (IB):

100994 PCT Amended Claims



(IB)

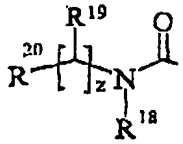
wherein:

X is $-N(R^{38})-$, $-N(R^{38})C(O)-$, $-O-$, and $-S(O)_a-$; wherein a is 0-2 and R^{38} is hydrogen or C_{1-4}alkyl;

R^{14} is hydrogen or C_{1-4}alkyl;

R^{15} and R^{16} are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, carbocyclyl or heterocyclic group; wherein R^{15} and R^{16} may be independently optionally substituted on carbon by one or more substituents selected from R^{41}; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{42};

R^{17} is selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxy, C_{1-10}alkanoyl, C_{1-10}alkanoyloxy, *N*-(C_{1-10}alkyl)amino, *N,N*-(C_{1-10}alkyl)$_2$amino, C_{1-10}alkanoylamino, *N*-(C_{1-10}alkyl)carbamoyl, C_{1-10}alkoxycarbonyl, *N,N*-(C_{1-10}alkyl)$_2$carbamoyl, C_{1-10}alkylS(O)$_a$ wherein a is 0 to 2, *N*-(C_{1-10}alkyl)sulphamoyl, *N,N*-(C_{1-10}alkyl)$_2$sulphamoyl, *N*-(C_{1-10}alkyl)sulphamoylamino, *N,N*-(C_{1-10}alkyl)$_2$sulphamoylamino, carbocyclyl, carbocyclylC_{1-10}alkyl, heterocyclic group, heterocyclylC_{1-10}alkyl, carbocyclyl-(C_{1-10}alkylene)$_e$-R^{43}-(C_{1-10}alkylene)$_f$- or heterocyclyl-(C_{1-10}alkylene)$_g$-R^{44}-(C_{1-10}alkylene)$_h$-; wherein R^{17} may be optionally substituted on carbon by one or more substituents selected from R^{47}; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{48}; or R^{17} is a group of formula (IC):



(IC)

wherein:

R^{18} is selected from hydrogen or C_{1-4}alkyl;

R^{19} is selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, carbocyclyl or heterocyclic group; where R^{19} may be independently optionally substituted on carbon by one or more substituents selected from R^{51}; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{52};

R^{20} is selected from halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxy, C_{1-10}alkoxycarbonyl, C_{1-10}alkanoyl, C_{1-10}alkanoyloxy, *N*-(C_{1-10}alkyl)amino, *N,N*-(C_{1-10}alkyl)$_2$amino, *N,N,N*-(C_{1-10}alkyl)$_3$ammonio, C_{1-10}alkanoylamino, *N*-(C_{1-10}alkyl)carbamoyl, *N,N*-(C_{1-10}alkyl)$_2$carbamoyl, C_{1-10}alkylS(O)$_a$ wherein a is 0 to 2, *N*-(C_{1-10}alkyl)sulphamoyl, *N,N*-(C_{1-10}alkyl)$_2$sulphamoyl, *N*-(C_{1-10}alkyl)sulphamoylamino, *N,N*-(C_{1-10}alkyl)$_2$sulphamoylamino, C_{1-10}alkoxycarbonylamino, carbocyclyl, carbocyclylC_{1-10}alkyl, heterocyclic group, heterocyclylC_{1-10}alkyl, carbocyclyl-(C_{1-10}alkylene)$_e$-R^{53}-(C_{1-10}alkylene)$_f$- or heterocyclyl-(C_{1-10}alkylene)$_g$-R^{54}-(C_{1-10}alkylene)$_h$-; wherein R^{20} may be independently optionally substituted on carbon by one or more R^{57}; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{58};

p is 1-3; wherein the values of R^{15} may be the same or different;

q is 0-1;

r is 0-3; wherein the values of R^{16} may be the same or different;

m is 0-2; wherein the values of R^{12} may be the same or different;

n is 1-2; wherein the values of R^{8} may be the same or different;

z is 0-3; wherein the values of R^{19} may be the same or different;

R^{21} is selected from hydrogen or C_{1-6}alkyl;

R^{22} and R^{23} are independently selected from hydrogen, hydroxy, amino, mercapto, C_{1-6}alkyl, C_{1-6}alkoxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2;

R^{24} is selected from hydrogen, hydroxy, C_{1-6}alkyl, C_{1-4}alkoxy and C_{1-6}alkanoyloxy;

R^{25} is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, *N*-(C_{1-4}alkyl)sulphamoyl and *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl; wherein R^{25}, may be independently optionally substituted on carbon by one or more R^{67};

R^{26}, R^{28}, R^{30}, R^{36}, R^{41}, R^{47}, R^{51} and R^{57} are independently selected from halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxy, C_{1-10}alkanoyl, C_{1-10}alkanoyloxy, C_{1-10}alkoxycarbonyl, *N*-(C_{1-10}alkyl)amino, *N,N*-(C_{1-10}alkyl)$_2$amino, *N,N,N*-(C_{1-10}alkyl)$_3$ammonio, C_{1-10}alkanoylamino, *N*-(C_{1-10}alkyl)carbamoyl, *N,N*-(C_{1-10}alkyl)$_2$carbamoyl, C_{1-10}alkylS(O)$_a$ wherein a is 0 to 2, *N*-(C_{1-10}alkyl)sulphamoyl, *N,N*-(C_{1-10}alkyl)$_2$sulphamoyl, *N*-(C_{1-10}alkyl)sulphamoylamino, *N,N*-(C_{1-10}alkyl)$_2$sulphamoylamino, C_{1-10}alkoxycarbonylamino, carbocyclyl, carbocyclylC_{1-10}alkyl, heterocyclic group, heterocyclylC_{1-10}alkyl, carbocyclyl-(C_{1-10}alkylene)$_e$-R^{59}-(C_{1-10}alkylene)$_f$- or heterocyclyl-(C_{1-10}alkylene)$_g$-R^{60}-(C_{1-10}alkylene)$_h$-; wherein R^{26}, R^{28}, R^{30}, R^{36}, R^{41}, R^{47}, R^{51} and R^{57} may be independently optionally substituted on carbon by one or more R^{63}; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{64};

R^{27}, R^{29}, R^{31}, R^{37}, R^{42}, R^{48}, R^{52}, R^{58} and R^{64} are independently selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, benzyl, phenethyl, benzoyl, phenylsulphonyl and phenyl;

R^{32}, R^{33}, R^{43}, R^{44}, R^{53}, R^{54}, R^{59} and $R^{60}$are independently selected from -O-, -NR^{65}-, -S(O)$_x$-, -NR^{65}C(O)NR^{66}-, -NR^{65}C(S)NR^{66}-, -OC(O)N=C-, -NR^{65}C(O)- or -C(O)NR^{65}-; wherein R^{65} and R^{66} are independently selected from hydrogen or C_{1-6}alkyl, and x is 0-2;

R^{63} and R^{67} re independently selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, methyl, ethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, methoxycarbonyl, formyl, acetyl, formamido,

acetylamino, acetoxy, methylamino, dimethylamino, *N*-methylcarbamoyl, *N,N*-dimethylcarbamoyl, methylthio, methylsulphinyl, mesyl, *N*-methylsulphamoyl and *N,N*-dimethylsulphamoyl; and

e, f, g and h are independently selected from 0-2;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; with the proviso that said compound is not:

1,1-dioxo-3-isopropyl-5-phenyl-8-[*N*-(propyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,4-benzothiazepine; or

1,1-dioxo-3-isopropyl-5-phenyl-7-iodo-8-[*N*-(propyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,4-benzothiazepine.

2. A compound of formula (I) according to claim 1 wherein M^1 is $-CH_2-$ and M^2 is $-CR^{22}R^{23}-$; or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

3. A compound of formula (I) according to claim 1 wherein M^1 is $-CH_2-$ and M^2 is $-NR^{24}-$; or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

4. A compound of formula (I) according to claim 1 or 2 wherein R^{22} and R^{23} are independently selected from hydrogen and hydroxy; or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

5. A compound of formula (I) according to claim 1 or 3 wherein R^{24} is hydrogen; or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

6. A compound of formula (I) according to any one of claims 1-5 wherein R^1 and R^2 are C_{1-4}alkyl; or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

7. A compound of formula (I) according to any one of claims 1-6 wherein v is 0; or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

8. A compound of formula (I) according to any one of claims 1-7 wherein R^4 and R^7 are hydrogen; or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

9. A compound of formula (I) according to any one of claims 1-8 wherein the R^5 or R^6 not selected from a group of formula (IA) is hydrogen or methylthio; or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

10. A compound of formula (I) according to any one of claims 1-9 wherein one of R^5 and R^6 is a group of formula (IA) (as depicted above); wherein:

Z is -O- or -$S(O)_b$-; wherein b is 0;

R^8 is hydrogen;

R^9 is hydrogen;

R^{10} and R^{11} are independently selected from hydrogen or carbocyclyl; wherein R^{10} and R^{11} may be independently optionally substituted on carbon by one or more substituents selected from R^{28};

R^{13} is a group of formula (IB) (as depicted above);

R^{14} is hydrogen;

R^{15} is hydrogen;

R^{17} is C_{1-10}alkyl; wherein R^{17} may be optionally substituted on carbon by one or more substituents selected from R^{47}; or R^{17} is a group of formula (IC) (as depicted above) wherein:

R^{18} is selected from hydrogen;

R^{19} is selected from hydrogen;

R^{20} is C_{1-10}alkyl; wherein R^{20} may be independently optionally substituted on carbon by one or more R^{57};

p is 1;

q is 0;

r is 0;

m is 0;

n is 1;

z is 1; and

R^{28}, R^{47} and R^{57} are independently selected from halo and hydroxy

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

11. A compound of formula (I) wherein:

M^1 is $-CH_2-$;

M^2 is $-CR^{22}R^{23}-$ and $-NR^{24}-$;

R^{22} and R^{23} are independently selected from hydrogen and hydroxy;

One of R^1 and R^2 is ethyl and the other is butyl;

v is 0;

R^4 and R^7 are hydrogen;

One of R^5 or R^6 is selected from a group of formula (IA) (as depicted above) and the other is hydrogen or methylthio;

Z is -O- or $-S(O)_b-$; wherein b is 0;

R^8 is hydrogen;

R^9 is hydrogen;

R^{10} and R^{11} are independently selected from hydrogen, 2-fluorophenyl or carbocyclyl;

R^{13} is a group of formula (IB) (as depicted above);

R^{14} is hydrogen;

R^{15} is hydrogen;

R^{17} is pentyl substituted by 5 hydroxy; or R^{17} is a group of formula (IC) (as depicted above) wherein:

R^{18} is selected from hydrogen;

R^{19} is selected from hydrogen;

R^{20} is pentyl substituted by 5 hydroxy;

p is 1;

q is 0;

r is 0;

m is 0;

n is 1; and

z is 1;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

12. A compound of formula (I) selected from:

(+/-)-trans-1,1-dioxo-3-ethyl-3-butyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*'-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine;

(+/-)-trans-1,1-dioxo-3-ethyl-3-butyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*'-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine;

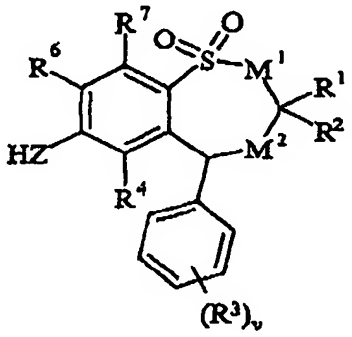
1,1-dioxo-3-ethyl-3-butyl-4-hydroxy-5-phenyl-7-(*N*-{α-[*N*'-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]-2-fluorobenzyl}carbamoylmethylthio)-2,3,4,5-tetrahydrobenzothiepine; or

1,1-dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-(*N*-{1-[*N*'-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]-1-(cyclohexyl)methyl}carbamoylmethylthio)-2,3,4,5-tetrahydrobenzothiepine;

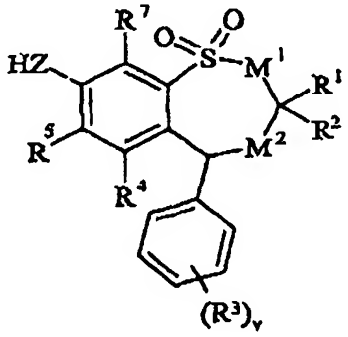
or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

13. A process for preparing a compound of formula (I) or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in anyone of claims 1-12, which process (wherein variable groups are, unless otherwise specified, as defined in claim 1) comprises of:

Process 1): for compounds of formula (I) wherein Z is -O-, -NR^a or -S-; reacting a compound of formula (IIa) or (IIb):



(IIa)



(IIb)

with a compound of formula (III):

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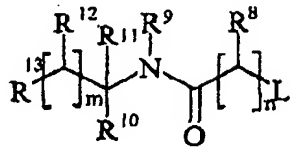
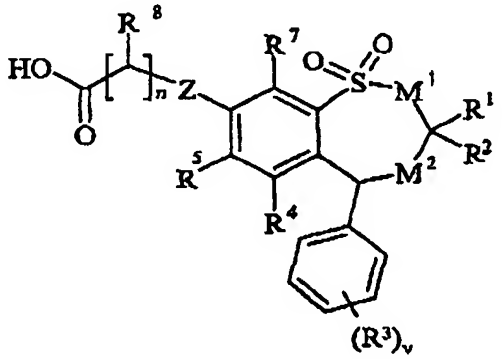


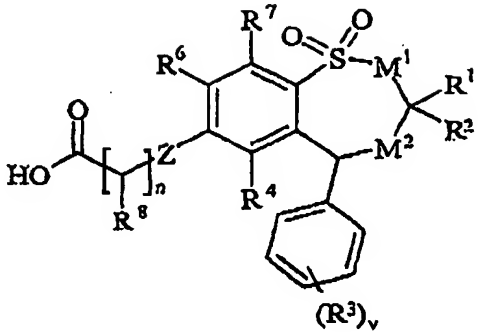
(III)

wherein L is a displaceable group;

Process 2): reacting an acid of formula (IVa) or (IVb):

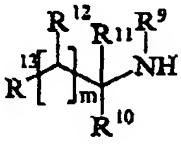


(IVa)



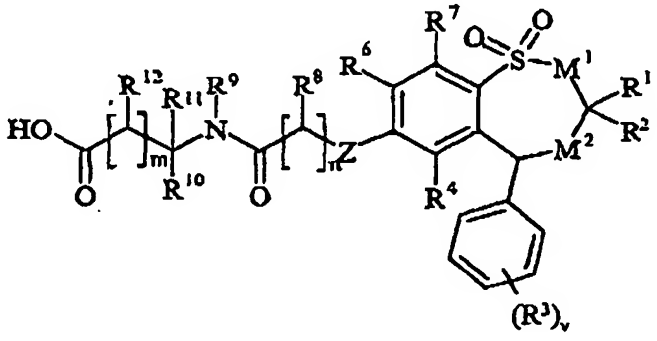
(IVb)

or an activated derivative thereof; with an amine of formula (V):



(V);

Process 3): for compounds of formula (I) wherein R^{13} is a group of formula (IB); reacting an acid of formula (VIa):



(VIa)

or (VIb):

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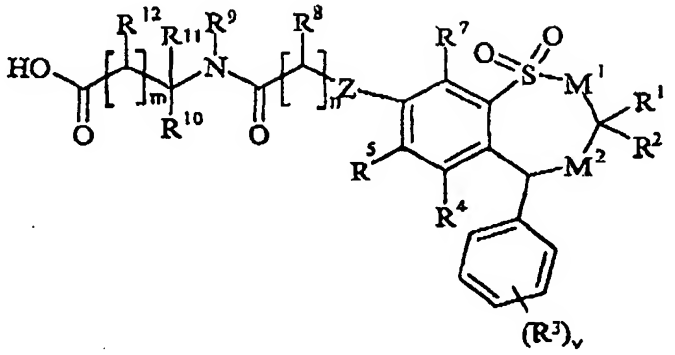
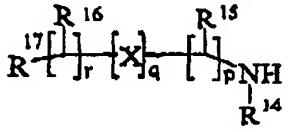


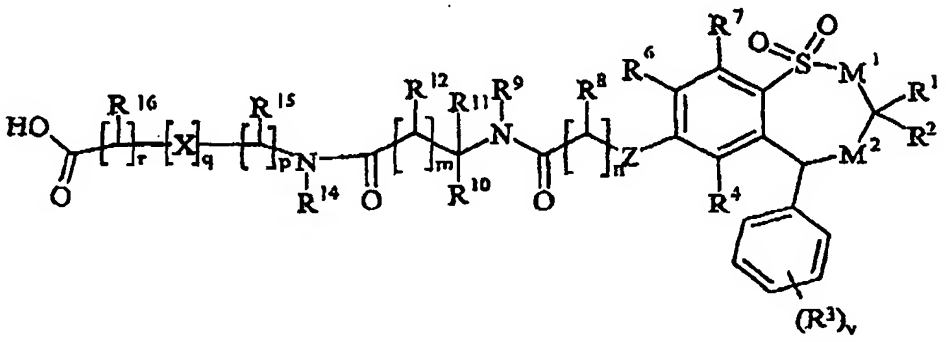
(VIIb)

with an amine of formula:



(VI)

Process 4): for compounds of formula (I) wherein R^{13} is a group of formula (IB) and R^{17} is a group of formula (IC); reacting an acid of formula (VIIIa):



(VIIIa)

or (VIIIb)

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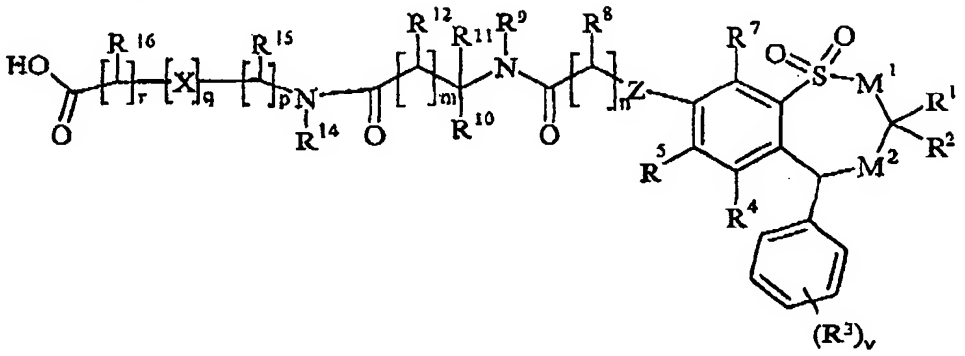
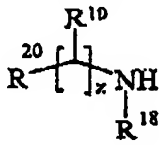


(VIIIb)

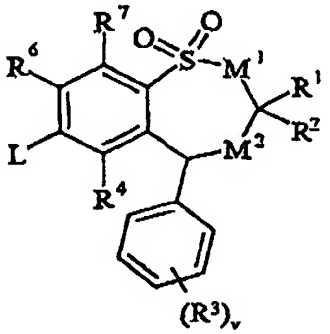
or an activated derivative thereof; with an amine of formula **(IX)**:



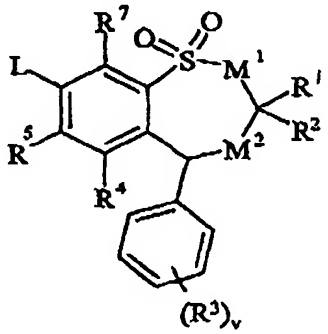
(IX)

or

Process 5) for compounds of formula **(I)** wherein one of R^5 and R^6 are independently selected from C_{1-6}alkylthio optionally substituted on carbon by one or more R^{25}; reacting a compound of formula **(Xa)** or **(Xb)**:



(Xa)



(Xb)

wherein L is a displaceable group; with a thiol of formula **(XI)**:

R^m-H

(XI)

wherein R^m is C_{1-6}alkylthio optionally substituted on carbon by one or more R^{25};

and thereafter if necessary or desirable:

i) converting a compound of the formula **(I)** into another compound of the formula **(I)**;

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ii) removing any protecting groups;
iii) forming a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug.

14. A compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 12 for use as a medicament.

15. A compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 12 for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man.

16. The use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 12 in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

17. A method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 12.

18. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 12, in association with a pharmaceutically-acceptable diluent or carrier.

19. A combination comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 12, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

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20. A combination comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 12, and a bile acid binder.

21. A combination comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 12, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder.

22. A combination according to claim 19 or claim 21 wherein the HMG Co-A reductase inhibitor is atorvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

23. A combination according to claim 19 or claim 21 wherein the HMG Co-A reductase inhibitor is rosuvastatin, or a pharmaceutically acceptable salt thereof.

24. A combination comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 12 and a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt thereof.

25. A composition according to claim 24 wherein the PPAR alpha and/or gamma agonist is (S)-2-ethoxy-3-[4-(2-{4-methanesulphonyloxyphenyl}ethoxy)phenyl]propanoic acid or a pharmaceutically acceptable salt thereof.